

Interface Prescribing Subgroup

DRUGS FOR DEMENTIA: INFORMATION FOR PRIMARY CARE

Cholinesterase inhibitors and Memantine are now classified as green (following specialist initiation) drugs by the Greater Manchester Medicines Management Group.

Who will diagnose and decide who is suitable for which drug?

Specialists will continue to diagnose, assess suitability and safety of drug treatment for patients referred to Memory Services. Specialists will counsel and inform patients of their diagnosis and treatment options. Specialists will then follow up the patients until the patient is stable on the maximum tolerated dose of medication, this is usually for a period of one to three months.

Who will increase the dose?

Patients are likely to be on the maximum tolerated dose of medication when they are discharged from the memory service. Should further information be required, the locality memory treatment services can be contacted.

Who will follow up the patients?

Once the patient is stable on the maximum tolerated dose of medication, specialists will discharge stable patients back to primary care. During the assessment period, specialists will identify patients with complex needs and refer onto other services. The memory service will continue to follow up for longer on a case by case basis, as need dictates.

Related NICE guidance

[NICE \(TAG 217\)](#) recommends that Acetylcholinesterase inhibitors are clinically cost effective and has recommended their use in mild to moderate Alzheimer's Disease. NICE also recommends they be considered for people with dementia with Lewy bodies and patients with Alzheimer's Disease irrespective of severity who have non cognitive symptoms and/or behavioural challenges causing significant distress or potential harm to the individual.

[NICE \(TAG 217\)](#) recommends memantine as an option for managing moderate Alzheimer's disease for people who cannot take AChE inhibitors, and as an option for managing severe Alzheimer's disease

Licensed Indication

Memantine is a glutamate receptor antagonist licensed for the treatment of moderate – severe Alzheimer's disease. Memantine is not licensed for use in combination with Acetylcholinesterase inhibitors.

Acetylcholinesterase inhibiting drugs are used in the treatment of Alzheimer's disease, specifically for mild to moderate disease. Rivastigmine is also used for mild to moderate dementia associated with Parkinson's disease. Donepezil, galantamine and rivastigmine reversibly antagonise the action of acetylcholinesterase increasing the concentration of acetylcholine released by functionally intact cholinergic neurones to facilitate cholinergic transmission. Galantamine also exhibits nicotinic receptor agonist properties.

Dosage and Administration

Donepezil: It is given initially at 5 mg once daily. After 1 month the treatment should be assessed, and the dose can be increased to a maximum of 10 mg once daily if necessary. It is recommended that the dose is given at bedtime to minimise

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likelihood of gastrointestinal (GI) symptoms. However if sleep disturbances are noted, particularly vivid nightmares, then a shift to morning dosing can resolve this.

Galantamine: The dose is initially 4mg twice daily for a minimum period of 4 weeks with a maintenance dose 8mg twice daily for a minimum of 4 weeks. This can be increased to 12mg twice daily after appropriate assessment of benefit & tolerability.

If no response to the higher dose or unable to tolerate, reduce to 8mg twice daily.

Where appropriate, the total daily dose may be converted to once daily administration using modified release formulations.

Galantamine should be taken after food to reduce the risk of cholinergic side effects (e.g. nausea, vomiting, diarrhoea). Administration with food slows rate of absorption but has no effect on total absorption. Modified release forms must be swallowed whole and not chewed.

Rivastigmine : The dose is initially 1.5 mg twice daily and may be increased in steps of 1.5 mg twice daily at intervals of at least 2 weeks according to tolerance up to a maximum dose of 6 mg twice daily. Rivastigmine increases gastric acid secretion and should be taken with food to minimise the effects of this.

Alternatively rivastigmine patches are available, initially using a 4.6-mg patch per day. This can be increased to a 9.5-mg patch per day for at least 4 weeks.

9.5 mg/24 h is the recommended daily effective dose which should be continued for as long as the patient continues to demonstrate therapeutic benefit. If well tolerated and only after a minimum of six months of treatment at 9.5 mg/24 h, the treating physician may consider increasing the dose to 13.3 mg/24 h in patients who have demonstrated a meaningful cognitive deterioration (e.g. decrease in the MMSE) and/or functional decline (based on physician judgement) while on the recommended daily effective dose of 9.5 mg/24 h.

See summary of product characteristics for further information on using patches.

Memantine: Initially 5mg daily for a minimum of seven days.

Increase by 5mg in weekly intervals to a maximum daily dose of 20mg.

Tablets should be administered once a day and should be taken at the same time every day.

What are the contraindications/ cautions for initiating these drugs?

Cholinesterase inhibitors are contraindicated in heart block and sick-sinus syndrome. They should be used in caution with those with other supraventricular conduction problems and arrhythmias, e.g. atrial fibrillation. An ECG is indicated prior to initiation and if patients develop bradycardia, syncope or palpitations during treatment to exclude heart block. Memantine is used as an alternative in these situations.

Oral cholinesterase inhibitors are used with caution in people with a history of upper GI ulceration and bleeding: Memantine, additional Proton Pump Inhibitor cover or Rivastigmine patches may be used as an alternative.

Caution is also advised in those with history of epilepsy or a pre-disposition to seizures.

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Cholinesterase inhibitors should be used with caution in people with asthma and COPD.

Galantamine is contraindicated in those with an eGFR of < 9 ml/min, and the dose of Memantine should be reduced to 10mg if eGFR is 30-49 ml/min then increased to 20mg if tolerated. If the patient's eGFR is 5-29 ml/min, a reduced maximum dose of 10mg may be required.

What are the main side-effects?

The most common side-effects of cholinesterase inhibitors are nausea, mild anorexia, fatigue, diarrhoea, muscle cramps and sometimes poor sleep. Additionally, the most common side effect of Memantine is constipation. Patients should be advised to take the medicine with food to minimise side effects. Side effects usually decrease with time.

Serious skin reactions (Stevens-Johnson syndrome and acute generalized exanthematous pustulosis) have been reported in patients receiving galantamine. It is recommended that patients be informed about the signs of serious skin reactions, and that use of galantamine be discontinued at the first appearance of skin rash.

Please refer to the BNF for further details.

Drug Interactions

Individuals being treated with drugs affecting cognitive function will require review as below before initiation of these drugs.

Alcohol misuse	Patients currently drinking unsafe amounts of alcohol will not be treated with cholinesterase inhibitors or memantine, but may be considered for treatment if they have Alzheimer's disease or Lewy Body Disease and their alcohol intake is reduced to be within safe limits.
Benzodiazepines	Consideration must be given to whether the benzodiazepines may be affecting cognitive function especially in large doses, if so they must be reduced gradually and stopped.
Non Steroidal Anti Inflammatory Drugs (NSAID)	Increased risk of acid production with Cholinesterase inhibitors review need for NSAID. Patients may need increased monitoring for gastric complications if using NSAID. See NB below
Drugs that may cause bradycardia e.g. digoxin, beta blockers	There is an increased risk of potentiation of bradycardia with cholinesterase inhibitors. This is particularly important in 'sick sinus syndrome' or AV block. Increased monitoring is required.
Tricyclic antidepressants have anticholinergic effects	Tricyclic antidepressants as an antidepressant: Consider changing to an SSRI/ SNRI or Mirtazapine if still requiring treatment. Individual drugs vary in their capacity to interact so check before prescribing an antidepressant. For example there is an interaction between paroxetine and galantamine, which may increase the levels of the cholinesterase inhibitor.
Tricyclic Antidepressants as an adjunct to pain control	If prescribed for pain in small dosage, and still required after review, continue with caution.
Other Anticholinergic drugs	Review the need for these drugs as they may oppose the effect of cholinesterase inhibitors.
Drugs with Cholinomimetic properties:	Peripherally Acting Cholinesterase inhibitors: Such as neostigmine or pyridostigmine. Cholinergic drugs e.g. pilocarpine.

NB: If patients are prescribed medication which increases the risk of gastric irritation, such as aspirin, NSAID, SSRI a proton pump inhibitor or equivalent should be prescribed concomitantly.

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Memantine:

Avoid concomitant use of ketamine, dextromethorphan and amantadine. Memantine possibly enhances the anticoagulant effect of warfarin so if these drugs are to be used concurrently additional INR monitoring should be carried out and dose adjusted accordingly. Drugs that increase the pH of the urine (e.g. sodium bicarbonate, carbonic anhydrase inhibitors) may reduce the elimination of memantine.

L-dopa, dopaminergic agonists and anticholinergics may be enhanced. Effects of barbiturates and antipsychotics may be reduced. Concomitant administration with antispasmodics, dantrolene or baclofen can modify their effects and dosage adjustment may be necessary.

Increased plasma levels possible with cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine.

Acetylcholinesterase inhibitors:

There are no specific dose changes which need to be made in relation to acetylcholinesterase inhibitors however it would be useful for prescribers to be aware of the following:

- Potent inhibitors of CYP3A4 (including ritonavir, clarithromycin and itraconazole) may raise donepezil and galantamine levels.
- Inducers of CYP3A4 (including carbamazepine, phenytoin, and rifampicin) may lower donepezil levels.
- Smoking tobacco increases the clearance of rivastigmine.

The risk of adverse effects, including bradycardia, may be increased if an acetylcholinesterase inhibitor is given with amiodarone or other antihypertensive/antiarrhythmic drugs.

Acetylcholinesterase inhibitors may antagonise effects of anticholinergic drugs and worsen Parkinsonian symptoms; this may induce or exacerbate extrapyramidal side effects.

Monitoring -

1. **Adverse effects:** Most common side effects are gastrointestinal disturbance (nausea, vomiting, and diarrhoea).
2. **Concurrent medication:** Medication should be reviewed at each visit in order to identify potential drug interactions.
3. **Renal and hepatic function:** Baseline creatinine and LFTs should be measured; Patients with renal or hepatic impairment should have doses titrated slowly and be monitored closely for adverse effects.
4. **Weight / BMI:** Weight loss is associated with Alzheimer's disease but acetylcholinesterase inhibitors are also reported to cause weight loss. Patients weighing <50kg may experience more adverse effects and are more likely to discontinue treatment as a result.
5. **Cardiovascular health:** Acetylcholinesterase inhibitors may have vagotonic effects so baseline cardiovascular function must be monitored before starting treatment and repeated when indicated, for example, when additional drugs with vagotonic effects are added or in the event of emerging cardiovascular problems.
6. **Cognitive, global functional and behavioural assessment:** Patients who continue on treatment should be reviewed at least annually by the GP. A cognition test may be done but, especially in more advanced dementia where benefits of cholinesterase inhibitors may cease

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to outweigh risks of continued treatment, an assessment of well-being and functioning is more important. Carers' views on the patient's condition at follow-up should be sought

When should the drug be stopped?

Drugs should be stopped if a patient developed an allergy or contra-indication to the medication. If a patient is not apparently gaining any benefit from the drug that may be an indication for stopping, however, in addition to treating the cognitive aspects of dementia, cholinesterase inhibitors and memantine have a role in behavioural and psychiatric changes in dementia and therefore, patients who are scoring low on cognitive testing may still benefit. Specialist advice should be sought on this decision from the locality memory treatment services

What happens if my patient's needs change or become more complex following discharge?

They can be re-referred back to the appropriate memory service via the normal referral pathway.

When to seek Specialist advice / review

You can get advice regarding patients taking drug treatments for dementia from the locality memory treatment services in addition to CCG community pharmacy support

In the majority of cases treatment will be initiated by a specialist in the care of people with dementia in line with NICE guidance. Following dose titration the specialist will recommend continuation treatment on the basis of tolerability & patient preference.

Tolerability may change over time consequent upon the ageing process and the emergence of medical co-morbidities and frailty. In this situation it may appropriate to reduce the dose or discontinue treatment &/or consider an alternative drug. It may be appropriate to make such decisions in consultation with the specialist who initiated treatment.

You may wish to seek advice in the following circumstances:

- Emergent concerns regarding tolerability
- To consider whether to discontinue treatment with a Cholinesterase Inhibitor at an advanced stage of the illness as outlined above.

Advice for patients having a general anaesthetic

Donepezil, Galantamine and Rivastigmine

Donepezil, Galantamine and Rivastigmine can enhance the effects of suxamethonium and the duration of the block may be prolonged. Donepezil and Rivastigmine can antagonise the effects of non-depolarising muscle relaxants such as atracurium, cisatracurium, mivacurium, pancuronium, rocuronium, vecuronium.

Memantine

No specific studies looking at use of memantine in patients undergoing surgery. In addition the company are not aware of any studies looking at memantine use with anaesthetics. Theoretically there may be a risk of pharmacotoxic psychosis if memantine is used concomitantly with ketamine. This is based on a report for amantadine as there are no reports with ketamine specifically (April 2011). Neuroleptics and anticholinergics used in surgical procedures may interact with memantine. The effect of neuroleptics may be reduced and the effect of anticholinergics may be enhanced

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although these interactions may be overcome by change of dose. See SPC for full list of drug interactions.

Drug	Situation	Advice
Donepezil	Planned operations	Stop 2 – 3 weeks before operation for complete wash out.
	Emergency operations	Inform the anaesthetist of potential of prolonged muscle relaxation.
	Post-operative	Re-introduce during post-surgical rehabilitation.
Rivastigmine	Planned Operations	Miss the last dose prior to surgery, i.e., if the operation is in the morning miss the previous night-time dose.
	Emergency operations	Inform the anaesthetist of potential of prolonged muscle relaxation.
	Post-operative	Re-introduce during post-surgical rehabilitation.
Galantamine	Planned Operations	stop two days before surgery for washout
	Emergency operations	Inform the anaesthetist of potential of prolonged muscle relaxation.
	Post-operative	Re-introduce during post-surgical rehabilitation
Memantine	Planned Operations	If a decision is made to discontinue memantine before surgery the total washout period would be 2 to 3 weeks. When to restart memantine will depend on the dose and half life of the drug used in surgery.

Guidance for GPs prescribing

The GP will monitor for ongoing side effects and discuss with Memory Service if any arise for advice on dose reduction, discontinuation etc. If a patient's cardiac health changes appropriateness of prescription will need to be discussed with the memory service and consideration for referral to cardiology.

- Provide regular prescriptions for cholinesterase inhibitors or memantine as per local guidance.
- Be aware of side effects and common drug interactions as documented in this guideline.
- Provide regular health checks including where relevant the review of clients with vascular dementia or mixed dementia and provision of advice about lifestyle.
- Inform specialist services of any relevant physical health problems at the earliest opportunity for those still open to specialist services or re-refer if necessary.
- If patient suffers any adverse reaction, GP should liaise with secondary care/specialist services.
- If patient develops bradycardia with symptoms on cholinesterase inhibitors, such as light-headedness or syncope, review any medication which may cause bradycardia, stop the drug if appropriate and notify Memory Clinic. If patient develops bradycardia without symptoms and if the rate is persistently less than 50, stop the cholinesterase inhibitor and notify Clinic, if rate is 50-60, continue drug and notify the memory Service.
- If patient develops second or third degree AV block, stop cholinesterase inhibitor, consider referral to cardiology and notify memory clinic.

Any patient who is currently prescribed an AChE and develops any cardiac disease or peptic ulcer disease (that the Specialists at the memory service are not aware of) please contact the memory service to discuss on going appropriateness of drug treatment.